Remarks

The specification has been amended throughout to correct the presentation of sequence identifiers, to correct the recitation of certain corporate names, and to correct typographical errors and minor errors of syntax. No new matter has been added by these amendments.

Claims 1-8 are currently pending in the application. Claims 1-8 are currently amended. Upon entry of the present amendments, claims 1-8 will be pending in this application. Claims 2-5, 7 and 8 are amended to appropriately refer to SEQ ID NOS. Claims 3 and 8 are amended to appropriately recite multiple dependency. Claims 4 and 5 are amended, *inter alia*, to replace the term "peptide-DNA complex" with "peptide vector." Claim 2-8 generally have been amended to correct syntax. Finally, claims 2, 4, 5 and 7 have been amended to include sequence variants of SEQ ID NO:1. Support for the amendments is found in the specification and claims as originally filed, and, with respect particularly to claim 2, 5 and 7, in the specification at page 6, lines 11-18.

It is submitted that no new matter has been introduced by the present amendments and new claims and entry of the same is respectfully requested. By the amendments, Applicant does not acquiesce to the propriety of any of the Examiner's rejections and does not disclaim any subject matter to which Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (1997).

Sequence Compliance

The Examiner requires correction in the specification of sequence identifiers (Office Action, page 2) pursuant to 37 C.F.R. 1.821(d). Applicants have amended each sequence identifier in the specification to read "SEQ ID NO:". Applicants respectfully submit that these corrections place the application in compliance with 37 C.F.R. 1.821(d).

Specification

The Examiner requires correction of the use of the term "ambion" in the specification at pages 11 and 12 (Office Action at page 3). Applicants have amended the paragraphs in which the term is present to capitalize, and to indicate that the term refers to a corporate entity. Applicants have similarly corrected recitation of "Takara" on page 12. The terms require no generic terminology.

Claim Objections

The Examiner has objected to claims 3 and 8 as depending inclusively, and not alternatively, on more than one claim. Applicants have amended claims 3 and 8 to

appropriately recite dependencies. Applicants respectfully request the Examiner withdraw the objection to claims 3 and 8 on this basis.

The Examiner has also objected to claims 2, 3, 7 and 8 as reciting "comprising" when "comprises" would be grammatically correct. Applicants have amended claims 2, 3, 7 and 8 accordingly. Applicants respectfully request the Examiner withdraw the objection to claims 2, 3, 7 and 8 on this basis.

The Rejection of Claims 1, 4 and 6 Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Examiner has rejected claims 1, 4 and 6 under 35 U.S.C. § 102(b) as allegedly anticipated by Nelson *et al.*, U.S. Patent No. 5,736,392 ("Nelson"; Office Action, pages 4-5). Applicants respectfully traverse.

Nelson teaches DNA complexed with a peptide wherein the peptide associates with a nucleic acid, either by means of a DNA binding group, or by direct interaction with the nucleic acid. However, Nelson specifically discloses that the protein and nucleic acid portions of the complex interact *noncovalently*. *See, e.g.*, col. 3, line 66 to col. 4, line 4 ("The methods of the present invention involve contacting a eukaryotic cell with a transfecting composition comprising a . . . peptide . . . wherein said peptide or modified peptide [*sic*] is non-covalently associated with the nucleic acid."); col. 4, lines 14-41 (exemplifying preferred composition embodiments); col. 8, lines 53-55 (defining "peptide-nucleic acid complex"); Example 7.

Applicants have amended claims 1 and 6 to recite that the recited linker is a double-stranded DNA molecule, one strand of which is covalently linked to the leader peptide. The purpose of this is clear from the disclosure; one strand of the linker is covalently attached to the leader peptide, while the other is covalently bound to the gene of interest; thus, separation of the leader peptide and gene of interest, for example, within a transfected cell, is accomplished by separating the two hybridized strands of the linker. *See* specification, page 8, lines 5-10.

Nelson does not teach that the nucleic acid disclosed therein is covalently attached to the peptide. Therefore, Nelson cannot anticipate claims 1 and 6 as amended. Applicants respectfully request the Examiner withdraw the rejection of claims 1 and 6 on this basis.

With respect to the rejection of claim 4 in view of Nelson, the Examiner apparently believes that "[t]he breadth of [claim 4] reads on any protein-DNA complex so long as at least one peptide, at least one nucleotide of SEQ ID NO:2 and at least one nucleotide of SEQ ID NO:3 are present in the complex." Office Action, page 4. Applicants respectfully traverse.

Applicants have amended claim 4 to clarify that the recited peptide-DNA complex comprises a DNA having the sequence shown in SEQ ID NO:2, and a DNA having the sequence shown in SEQ ID NO:3. Thus, the claim as amended requires that the nucleic acid sequences of SEQ ID NO: 2 and SEQ ID NO: 3 be present in the complex.

Nelson does not disclose the sequences of SEQ ID NO:2 or SEQ ID NO:3. Moreover, Nelson does not disclose the sequence of SEQ ID NO:1, or the variants thereof, as recited in claim 4 as amended. Therefore, Nelson cannot anticipate claim 4 as amended. Applicants respectfully request the Examiner withdraw the rejection of claim 4 on this basis.

The Rejection of Claims 6-8 Under 35 U.S.C. § 112, ¶ 1 Should be Withdrawn

The Examiner has rejected claims 6-8 under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled for *in vivo* methods (Office Action, pages 5-9. Applicants respectfully traverse.

Analysis of enablement requires a determination of whether the "disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." MPEP 2164.01 at page 2100-178. One skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990). The standard for determining whether a claim is enabled or not is whether it requires undue experimentation to practice. *Id.*; *see also Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916); *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). In *Wands*, the Federal Circuit outlined several non-exclusive factors to consider in a determination of whether claims were enabled, including: A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In *Wands*, the Federal Circuit held that a particular method requiring substantial experimentation was nonetheless enabled, because the experimentation was routine.

In support of the rejection, The Examiner states that:

> Applicant has not provided any working examples in the specification toward a method of transferring a nucleic acid encoding a protein of interest to target cells *in vivo*. The disclosure is limited to a general discussion of the peptide-vector use for gene transfer in addition to examples discussing the synthesis of the

vector, preparation of marker genes and extraction of mRNA to measure transcription of the marker gene.

Office Action, page 7 (citing specification, pages 10-13). The Examiner further cites several articles from 1997-1999[1] stating that "progress in developing gene therapy is slow," that (as of 1998) "the efficiency of gene transfer and expression in human patients is . . . still is disappointingly low," that there are "inherent difficulties [in] transfecting cells *in vivo* by targeted delivery mechanisms" and that "no approach has been fully successful for *in vivo* gene transfer." Office Action at pages 6-7. Applicants respectfully traverse.

With respect to the Examiner's first point, the instant specification does, indeed provide a working example of *in vivo* transfer of a nucleic acid to a target cell. Example 4 describes the *in vivo* transfer of a peptide vector containing a green fluorescent protein (GFP)-coding sequence to different tissues in mouse. A peptide vector containing a GFP-coding sequence, constructed according to Examples 1-3 was injected into male mice. Page 11, lines 17-18. The mouse was sacrificed six days later, and mRNA was extracted from brain and muscle. Page 11, lines 19-20. The mRNA was reverse-transcribed, and PCR was performed on the resulting cDNA using GFP-specific primers. Page 12, lines 1-15. PCR showed that GFP was efficiently expressed in brain and muscle. Applicants therefore have demonstrated the *in vivo* efficacy of the disclosed peptide vector.

With respect to the state of the art, some in the art have written about perceived difficulties in achieving *in vivo* gene transfer; however, the reported difficulties lay with older means of gene transfer, primarily the use of viral vectors (*see*, *e.g.*, Verma). It is clear that much of the current difficulty regarding gene therapy is inherent in the use of viral vectors, wherein one must consider the toxicity of the virus, placement of a transgene into the appropriate segment or portion of the host virus genome, efficiency of packaging, non-transfection of certain cell types, communicability, development of immunity to certain viruses (such as adenoviruses), etc. (*see generally* Verma). In other words, existing viral vector delivery systems rely on, and suffer from, the complexities of viral infective physiology. It is because of these problems that Anderson suggests that, in the future, non-viral gene delivery systems will be the delivery method of choice. (Anderson, page 28, right column).

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[1] Verma and Somla, *Nature* 389:239-242 (1997) ("Verma"); Anderson, *Human Gene Ther.* 392 supp. 1998, pages 25-30 ("Anderson"); and Palu *et al.*, *J. Biotech* 68:1-13 (1999) ("Palu").

The peptide vector of the present invention, in contrast, represents a new, far simpler approach that does not depend upon viral vectors. Rather, the peptide vector of the current invention depends largely on the ability of a leader peptide (SEQ ID NO:1, and variants thereof, as described on page 6 of the specification) to interact with the host cell surface. Use of the peptide vector to carry a nucleic acid sequence of interest across a host cell membrane is far simpler than engineering a virus to do the same; thus, the amount of experimentation required to adapt the described vector to various nucleic acid sequences of interest and various hosts is, in turn, far simpler. Applicants have provided example leader peptides (*see* page 6) and a straightforward method of linking the desired gene, to be transported into a recipient cell, to the leader peptide (*see* pages 6-7). Introduction of the peptide vector to the recipient is accomplished by simple injection, and results in expression of the gene of interest within the recipient (Example 4). The invention of claims 6-8 is, therefore, sufficiently enabled.

Relying upon an established protein-mediated interaction with a target cell, the present invention also avoids problems inherent in the reliance upon random transfection methods dependent upon simple physical interactions, such as the complexing of a nucleic acid with a cationic lipid (*see, e.g.*, Nelson).

Given that the current invention and the gene delivery methods discussed by the cited references are so different, the problems detailed in those references do not apply to the claimed method. This view is supported by the specification's showing that the peptide vector did, in fact, successfully transport a foreign gene into the cells of a living organism (*see* Example 4). Thus, a person of skill in the art would be able to construct and use the vector of the instant invention without undue experimentation. Applicants therefore respectfully submit that claims 6-8 are sufficiently enabled, and request that the Examiner withdraw the rejection of these claims on this basis.

The Rejection of Claims 1-4 and 6-8 Under 35 U.S.C. § 112, ¶ 1 Should be Withdrawn

The Examiner has rejected claims 1-4 and 6-8 under 35 U.S.C. § 112, ¶ 1 as lacking sufficient written description in their recitation of the term "gene." Office Action, pages 8-9. The Examiner suggests substitution of "nucleic acid sequence" for "gene." Page 9. Following the Examiner's suggestion, Applicants have amended independent claims 1 and 6 to recite "nucleic acid sequence" rather than "gene." Applicants respectfully submit that claims 1 and 6, as amended, have sufficient written description support in the specification. Claims 2-4, dependent from claim 1, and claims 7 and 8, dependent from claim 6, likewise

sufficiently described in the specification. Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-4 and 6-8 on this basis.

The Rejection of Claims 4 and 5 Under 35 U.S.C. § 112, ¶ 2 Should be Withdrawn

The Examiner has rejected claims 4 and 5 under 35 U.S.C. § 112, ¶ 2 as indefinite. Office Action at page 9. Applicants traverse as follows.

The Examiner believes claim 4 to be indefinite in its recitation of "a peptide of" SEQ ID NO:1 and "a DNA of" SEQ ID NOS:2 and 3. Office Action at page 9. The Examiner believes that it is thus unclear whether the Applicant claims à single peptide, a single nucleic acid, a fragment of the peptide, a fragment of the nucleic acids, or the full-length peptide and nucleic acids. Applicants have amended claim 4 to clarify that the peptide has the sequence as shown in SEQ ID NO:1, and that the linker DNA has a DNA having the sequence shown in SEQ ID NO:2 and a DNA having the sequence shown in SEQ ID NO:3. Claim 4 as amended is thus definite. Applicants respectfully request that the Examiner withdraw the rejection of claim 4 on this basis.

The Examiner believes that claim 5 is indefinite in its recitation of "the peptide" and "the DNA of" because there is no antecedent basis for these terms. Applicants have amended claim 5 to recite "a peptide" and "a nucleic acid." Claim 5 as amended is thus definite. Applicants respectfully request that the Examiner withdraw the rejection of claim 5 on this basis.

CONCLUSION

Applicant respectfully requests that the above remarks be entered in the present application file. An early allowance of the present application is respectfully requested.

No fee is believed due for this Amendment, other than the extension of time fee. However, if a fee is due, please charge such fee to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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